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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/214,009	05/07/1999	NICO JOHANNES C M BEEKMAN	3898US	6111

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EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/214,009	BEEKMAN ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,9,10 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,9,10 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 09/30/03 in response to the non-final Office Action mailed 05/01/03.

Status of Claims

2) Claims 1 and 3 have been amended via the amendment filed 09/30/03.

Claims 1, 3-6, 9, 10 and 12 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

5) The rejection of claim 1 made in paragraphs 24(a) and 24(b) of the Office Action mailed 05/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

6) The rejection of claim 3 made in paragraph 24(c) of the Office Action mailed 05/01/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

7) The rejection of claims 4-6, 9, 10 and 12 made in paragraph 24(d) of the Office Action mailed 05/01/03 under 35 U.S.C § 112, as being indefinite, is withdrawn in light of Applicants' amendments to the base claim.

Rejection(s) Maintained

8) The rejection of claims 1, 3, 4 and 12 made in paragraph 25 of the Office Action mailed 05/01/03 under 35 U.S.C § 102(e) as being anticipated by Yatvin *et al.* (US 6,339,060), is maintained for reasons set forth therein and herebelow.

Applicants contend that Yatvin's invention is directed to an improved method of delivering

biologically-active compounds into phagocytic cells, but do not disclose a vaccine as required by claim 1. Applicants state that Yatvin *et al.* define a 'biologically-active compound' as encompassing all naturally-occurring or synthetic compounds capable of eliciting a biological response or having an effect, either beneficial or cytotoxic. Applicants allege that these compounds are intended to include, but are not limited to all varieties of drugs as well as peptides including antimicrobial peptides. Applicants submit that a vaccine including an antigen as recited in instant claims is not included in this biologically active compound. Applicants point to column 23, lines 1-4 of Yatvin *et al.* and acknowledge that Yatvin *et al.* disclosed the weak linker functionality in their composition to be thioester, but argue that no working examples of Yatvin *et al.* disclose an 'antigen' linked to a fatty acid or fatty-acid peptide carrier with a thioester bond. Applicants state that Example II does not disclose an antigen linked to a fatty acid or a fatty acid-peptide carrier by a thioester bond and therefore Yatvin's disclosure is non-enabling. Applicants submit that claims 3, 4 and 12, at the very least, are not anticipated.

Applicants' arguments have been carefully considered, but are non-persuasive. First, it should be noted that the term 'vaccine' in the instant claims represents the intended use of the product and has no patentable weight. As set forth in paragraph 25 of the Office Action mailed 05/01/03, Yatvin *et al.* disclosed a composition comprising a conjugate of a biologically active compound linked to a polar lipid in a cleavable manner wherein the biologically active compound is specifically or non-specifically cleaved *in vivo* in a mammal under physiological conditions (see abstract; claims; and first two paragraphs under 'Summary of the Invention' in columns 7 and 8). A pharmaceutical composition comprising the conjugate in a pharmaceutically acceptable carrier is taught which is administered to a human (see claims 49, 69 and 71). The biologically active compound is an 'antigenically active' peptide; a toxin, such as, diphtheria toxin, or a peptide, such as, a defensin peptide (see claims; first paragraph in column 11; and Example 2). The toxin is man-made, i.e., synthetic (see first paragraph in column 19). One of the weak linker functionalities which is cleaved *in vivo* under specific conditions is thioester (see paragraph bridging columns 22 and 23). The lipid is phosphatidyl choline, phosphatidyl serine, phosphatidyl glycerol etc. (see claims). The linker functional group covalently links the biologically active compound to a polar lipid and is designed to facilitate, control, modulate and regulate the release of the biologically-active compound at a desired

target site (see last two full paragraphs in column 22). Contrary to Applicants' assertion, one of skill in the art would readily understand that a toxin, such as, diphtheria toxin, or a peptide, such as, a defensin peptide, would inherently serve as an antigen and an immunogen, absent evidence to the contrary. An antimicrobial peptide such as the one described in claims and Example 2 is described as an 'antigenically-active peptide' and therefore, qualifies as a peptide antigen or a hapten. Therefore, the prior art composition comprising a biologically active antigenic diphtheria toxin or defensin peptide is viewed as inherently being capable of serving as a vaccine or immunogen. Furthermore, working Examples in Yatvin's patent are not meant to be limiting, but represent non-limiting Examples or disclosure. Yatvin's specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. A prior art patent does not have to provide a working example for every embodiment in order to be enabled. Given the explicit disclosure of Yatvin *et al.* of the use of weak thioester as one of the linkers in their composition, one of skill in the art is able to at once envisage a conjugate composition comprising the thioester-containing biologically active diphtheria toxin or defensin peptide antigen linked to a polar lipid. The weak functional linkers to be used for linking the biologically active compounds to polar lipids are expressly taught by Yatvin *et al.* as linkers that are cleaved under specific conditions (see paragraph bridging columns 22 and 23). Yatvin's composition is administered to a human, i.e., *in vivo* administration. Clearly, Yatvin *et al.* do not teach away from the invention.

With regard to the alleged lack of an enabling disclosure of thioester linkage in a vaccine, it should be noted that the conventional use of thioester to couple a bacterial antigen to a bacterial protein to produce an immunogenic vaccine was well known in the art at the time of the instant invention. For instance, Heath *et al.* (US 5,356,622) taught conjugating an antigenic component to a carrier to enhance its immunogenicity and to produce a vaccine by 'directly' coupling or conjugating the antigen to the carrier via the conventionally used 'thioester' bonds (see abstract; and paragraph bridging columns 5 and 6). Similarly, Pier (US 5,502,039, issued 03/26/1996 and filed 06/11/1994) taught the use of thioester for coupling *Ps. aeruginosa* alginic acid to a protein carrier to produce a vaccine that elicited opsonizing antibodies *in vivo* (see abstract; and second full paragraph in column 10). Heath *et al.* and Pier are cited herein solely for the purpose of rebutting Applicants' arguments,

to reflect the state of the art at the time, and to establish that Yatvin's disclosure is fully enabling. Yatvin's antigen linked to a fatty acid or fatty-acid peptide carrier with a thioester bond inherently qualifies as a 'vaccine' since it was well known in the art at the time that peptide-fatty acid conjugates served both as an adjuvant-carrier-vaccine system and as a drug-delivery system. For instance, Flinn *et al.* (*Biochem. Soc. Trans.* 22: 1055-1058, 1994) taught a composition comprising an LHRH peptide directly conjugated to a lipidic or fatty amino acid via a biologically or chemically unstable linkage, wherein the fatty amino acid enhances the antibody response to the peptide immunogen (see pages 1055 and 1057). Flinn *et al.* taught that their low molecular mass carrier/adjuvant systems can be linked to antigens to yield 'immunogens for antibody production without further additives'. Most importantly, Flinn *et al.* taught that their product 'could be used as a combined adjuvant-carrier-vaccine system, as well as drug-delivery system' (see page 1057). Thus, it is understood that Yatvin's system serves both as a drug delivery system and as a vaccine.

9) The rejection of claims 1, 3-5, 9, 10 and 12 made in paragraph 26 of the Office Action mailed 05/01/03 under 35 U.S.C § 103(a) as being unpatentable over Chang *et al.* (US 5,149,782, already of record) in view of Yatvin *et al.* (US 6,339,060, already of record), is maintained for reasons set forth therein and herebelow.

Applicants submit the same arguments as discussed above with regard to the disclosure of Yatvin *et al.* Applicants contend that a *prima facie* case of obviousness cannot be established since no suggestion or motivation exists to combine the cited references. Applicants state that Chang *et al.* teach away from Yatvin *et al.* Applicants cite case law and submit that Yatvin *et al.* disclosed the delivery of a biologically-active compound to phagocytic cells through conjugating the compound with a microparticle via a cleavable linker moiety, and Chang *et al.* disclosed the irreversible linking of a membrane blending agent to a macromolecular drug. With this, Applicants conclude that since Chang *et al.* discloses the use of an irreversible linkage, one of ordinary skill in the art would not be motivated to combine the teaching of Chang *et al.* with Yatvin *et al.* which uses a cleavable linker moiety. Applicants further argue that neither Yatvin *et al.* nor Chang *et al.* teach or suggest the preparation of a vaccine, or an antigen linked to a fatty acid or fatty acid peptide carrier with a thioester bond.

Applicants' arguments have been carefully considered, but are non-persuasive. Applicants'

remarks on Yatvins' disclosure or lack thereof, are addressed above. Applicants are incorrect in stating that Chang's linkage is an irreversible linkage. As set forth in paragraph 26 of the Office Action mailed 05/01/03, Chang *et al.* disclosed therapeutic conjugates comprising an antigen, such as, a protein, polypeptide, synthetic peptides, glycoprotein or nucleic acid, coupled to a palmitic acid or other fatty acids of varying length via a linkage that is cleavable (i.e., labile) under appropriate conditions, for example, conditions extant at the target site (i.e., physiological conditions). Chang *et al.* taught that the linkage can be of cleavable (i.e., reversible) type (see column 8, lines 2 and 3) such as a disulfide linkage. See claims, claims 1, 2, 7, 10 and 11 in particular; column 2, lines 2-49; column 3, lines 9-13 and 17 and 18; column 3, lines 56 and 57; column 5, lines 9-23; and column 6, lines 31-45. Peptides that are used are synthetic (see column 3, lines 56 and 57). Chang *et al.* taught that cleavable bonds can also be constructed taking advantage of the slight acidic pH in target tissues (see third full paragraph in column 6). Two or more membrane blending agents (i.e., for example, peptide-peptide-fatty acid) can be coupled to a blocking agent via a cleavable linkage so that the blocking agent gets released (see column 2, lines 7-12 and 45-47). The blocking agent can be a monoclonal antibody, a ligand for a cell surface receptor or a short peptide (see column 2, lines 27-35 and 39-40). The blocking agent can also be a targeting agent such as, a **hormone** or growth factor which selectively directs the molecular conjugate to an appropriate target, (see column 6, lines first full paragraph). The composition is used *in vivo* (i.e., administered to a subject) for therapeutic and diagnostic purposes (see column 7, second full paragraph). That the therapeutic conjugate is administered (see column 6, lines 41-45) indicates that it was contained in a pharmaceutically acceptable carrier. Yatvin *et al.* is properly used in the obviousness rejection since Yatvin *et al.* taught the use of the cleavable linker moiety, thioester. One of skill in the art would readily understand from Chang's disclosure that Yatvin's thioester bond qualifies as a cleavable bond that can be constructed by taking advantage of the slight acidic pH in target tissues. It should be noted that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught. See *In re Nilssen*, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). The test of obviousness is not express suggestion of the claimed invention in any and all of the references, but rather what the references taken collectively would reasonably have suggested to those of ordinary skill in the art presumed to be familiar with them. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871,

881 (CCPA 1981).

10) The rejection of claims 1, 3-5 and 12 made in paragraph 27 of the Office Action mailed 05/01/03 under 35 U.S.C § 103(a) as being unpatentable over Shen *et al.* (US 5,907,030, filed 1995, already of record) in view of Yatvin *et al.* (US 6,339,060, already of record), is maintained for reasons set forth therein and herebelow.

Applicants allege that a '*prima facie* case of obviousness' cannot be established since neither Shen *et al.* nor Yatvin *et al.* alone or in combination teaches or suggests all of the elements of independent claim 1, or a 'vaccine'. Applicants contend that Shen *et al.* is limited to fatty acid-containing product with disulfide linkages that are employed for delivery of the sulfhydryl-containing compounds to mammalian cells, and that Shen does not suggest or motivate a vaccine. Applicants submit that Shen *et al.* is limited to the use of disulfide linkages and Yatvin *et al.* does not have an enabling disclosure of a thioester bonds in a working example. Applicants admit that Yatvin *et al.* mention of a thioester bond.

Applicants' arguments have been carefully considered, but are non-persuasive. As explained above, the disclosure Yatvin *et al.* cannot be dismissed as non-enabling for the sole reason that a working example involving the conventionally used thioester bond is lacking. The term 'vaccine' represents the intended use of the claimed product. With regard to Applicants' remarks on Shen *et al.*, if Shen *et al.* taught thioester linkage in their product, then Shen *et al.* would have been applied under 35 U.S.C § 102. As set forth in paragraph 27 of the Office Action mailed 05/01/03, Shen *et al.* disclosed a labile fatty acid-peptide or protein conjugates containing a reversible biodegradable bond, the breakage of which releases the peptide or protein compound *in vivo*. Shen's conjugate is contained in pharmaceutically acceptable carrier or adjuvants and is administered to a mammal in an aqueous solution. Shen *et al.* also disclosed a method of producing a palmityl disulfide conjugate of BBI protein (see columns 11 and 13) which was administered to mice (see Example 4). The reduction of BBIssPal conjugate with reducing agent caused the detachment of the palmitic acid from the conjugate (see column 13, lines 49 and 50). As fully explained in paragraph 27 of the Office Action mailed 05/01/03, Shen *et al.* and Yatvin *et al.* are properly combined and/or applied under 35 U.S.C § 103(a). The rejection stands.

11) The rejection of claim 6 made in paragraph 28 of the Office Action mailed 05/01/03 under 35

U.S.C § 103(a) as being unpatentable over Chang *et al.* (US 5,149,782, already of record) or Shen *et al.* (US 5,907,030, filed 1995, already of record) as modified by Yatvin *et al.* (US 6,339,060) as applied above to claims 1, 3 and 4 and further in view of Russell-Jones *et al.* (WO 91/02799, already of record) or Meloen *et al.* (US 6,284,733, already of record) (Meloen *et al.*, '733), is maintained for reasons set forth therein and herebelow.

With regard to Yatvin *et al.*, Applicants submit the same arguments as above. Applicants argue that none of the cited references teach or suggest a peptide having the exact amino acid sequence of SEQ ID NO: 1 and therefore a *prima facie* case of obviousness has not been established.

Applicants' arguments have been considered, but are non-persuasive. Meloen *et al.* do in fact teach Applicants' amino acid SEQ ID NO: 1 (see column 9, Example 1). For reasons set forth above and in paragraph 28 of the Office Action mailed 05/01/03, the rejection is proper and is maintained.

Relevant Prior Art

12) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- The use of thioester to couple a bacterial antigen to a bacterial protein to produce an immunogenic vaccine was well known in the art. For instance, Pier (US 5,502,039, issued 03/26/1996 and filed 06/11/1994) taught the use of thioester for coupling *Ps. aeruginosa* alginic acid to a protein carrier to produce a vaccine that elicited opsonizing antibodies *in vivo* (see abstract; and second full paragraph in column 10).
- Heath *et al.* (US 5,356,622) taught conjugating an antigenic component to a carrier to enhance its immunogenicity and to produce a vaccine by directly coupling or conjugating the antigen to the carrier via the conventionally used thioester bonds (see abstract; and paragraph bridging columns 5 and 6).
- Thioester as a cleavable linker in a vaccine system was well known in the art at the time of the invention. For instance, Yau *et al.* (US 5,541,287, issued 06/30/1996 and filed 11/22/1994) disclosed that thioester linkers are cleavable linkers which are acid sensitive and which are hydrolytically cleaved under acidic or basic conditions and by enzymes such as esterases (see paragraph bridging columns 19 and 20; and last paragraph in column 20). Yau *et al.* taught the use of thioester linkers for delivery of therapeutic agents (see abstract).

- Toth *et al.* (*J. Drug Target* 2: 217-239, 1994) taught a lipid or fatty amino acid and peptides conjugated to a variety of biologically active compounds, including LHRH or TRH, via a biologically or chemically unstable linkage (see abstract).

- Similarly, the covalent coupling of a peptide antigen such as LHRH was well known in the art at the time of the invention. For instance, Ladd *et al.* (US 5,843,446, filed 05 June 1995) taught that in order to avoid protein carrier-induced immune suppression, LHRH can be covalently linked to an immune enhancer or a fatty acid adjuvant such as Pam3Cys, which elicits significant adjuvanting responses to the peptide (see entire document, especially section 6 in columns 11-16).

- Flinn *et al.* (*Biochem. Soc. Trans.* 22: 1055-1058, 1994) taught a composition comprising an LHRH peptide directly conjugated to a lipidic or fatty amino acid via a biologically or chemically unstable linkage, wherein the fatty amino acid enhances the antibody response to the peptide immunogen (see pages 1055 and 1057). The parent LHRH is released from the prior art LHRH lipidic conjugate during incubation with Caco-2 cell homogenates by enzyme action and exhibited enhanced stability (see paragraph bridging pages (1057 and 1058). Flinn *et al.* taught that the lipopeptides taught by them constitute efficient low molecular mass carrier/adjuvant systems, which can be linked to antigens to yield 'immunogens for antibody production without further additives'. Most importantly, Flinn *et al.* taught that their system 'could be used as a combined adjuvant-carrier-vaccine system, as well as drug-delivery system' (see page 1057).

Remarks

13) Claims 1, 3-6, 9, 10 and 12 stand rejected.

14) **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The TC 1600 facsimile center receives transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

16) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347 until January 2004 and (571) 272-0854 beginning February 2004. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January, 2004

SD
S. DEVI, PH.D.
PRIMARY EXAMINER